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GRANT NUMBER DAMD17-97-1-7303

TITLE: MHC Genes and Breast Cancer

PRINCIPAL INVESTIGATOR: Shiv S. Pillai, M.D., Ph.D.

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, Massachusetts 02114

REPORT DATE: September 1998

TYPE OF REPORT: Annual

PREPARED FOR: Commanding General
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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| REPORT DOCUMENTATION PAGE | | | Form Approved OMB No. 0704-0188 | |
|---|--|--|---|--|
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| 1. AGENCY USE ONLY (Leave blank) | 2. REPORT DATE September 1998 | 3. REPORT TYPE AND DATES COVERED Annual (15 Aug 97 - 14 Aug 98) | | |
| 4. TITLE AND SUBTITLE MHC Genes and Breast Cancer | | 5. FUNDING NUMBERS DAMD17-97-1-7303 | | |
| 6. AUTHOR(S) Shiv S. Pillai, M.D., Ph.D. | | | | |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Massachusetts General Hospital Boston, Massachusetts 02114 | | 8. PERFORMING ORGANIZATION REPORT NUMBER | | |
| 9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012 | | 10. SPONSORING / MONITORING AGENCY REPORT NUMBER | | |
| 11. SUPPLEMENTARY NOTES <div style="text-align: center; font-size: 2em; font-weight: bold;">1 9 9 9 0 2 2 5 2 0 5</div> | | | | |
| 12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited | | 12b. DISTRIBUTION CODE | | |
| 13. ABSTRACT (Maximum 200 words) The goal of this study is to molecularly type all HLA class II genes in patients with breast cancer and in ethnically matched controls, in order to ascertain whether the inheritance of any of these genes contributes to susceptibility or resistance to breast cancer. Detailed molecular typing of DPB, DQB, and DRB1, 3, 4, and 5 alleles was performed on 144 controls. DNA was isolated from 70 freshly selected and cultured lymphoblastoid cell lines derived from patients with breast cancer. Molecular typing of DRB1, 3, 4, and 5 alleles was also performed on these patients. While preliminary results support earlier studies indicating a high frequency of DRB1*0701 in patients with breast cancer, clearly a larger analysis must be completed before attempting to statistically evaluate this information. | | | | |
| 14. SUBJECT TERMS Breast Cancer HLA Class II genes | | 15. NUMBER OF PAGES 14 | | |
| | | 16. PRICE CODE | | |
| 17. SECURITY CLASSIFICATION OF REPORT Unclassified | 18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified | 19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified | 20. LIMITATION OF ABSTRACT Unlimited | |

FOREWORD

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Shiv Pillai
PI - Signature

9/07/98
Date

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INTRODUCTION

This study is based on preliminary results suggesting that the inheritance of the HLA (Human Leukocyte Antigen) class II DRB1* 0701 allele is linked to breast cancer in women under the age of 40. This data, if supported in a larger and more complete study (involving the genotyping of all HLA class II genes), would lend credence to the notion that immunogenetic factors contribute to the development of breast cancer.

BODY

This application was funded last year, two years after the Preliminary Results were included in the original application (submitted in 1995). Since not all the DNAs from the group of patients examined in our preliminary studies were still available (having been used by the Center for Cancer Risk Analysis at MGH for other studies on the genetics of breast cancer), we resumed most of our studies from scratch. Lymphoblastoid cell lines from a fresh but partially overlapping set of breast cancer patients under the age of 40 were thawed and cultured. DNA was isolated, and totally fresh analyses were performed, even for generic DRB typing. The earlier typing cited in the preliminary results from over 3 years ago, was performed largely by Dr. David Forcione, when he was a medical student working part time in the laboratory. Subsequent typing has been performed over the past year by new personnel who have been trained after the initiation of funding. Given these constraints, we have nonetheless completed a significant portion of the project, starting from scratch.

We have completed a detailed analysis of all DRB1, DRB3, DRB4, DRB5, DPB1 and DQB1 alleles for 144 control subjects. Data from 93 of these has been reviewed and is listed in Tables I through IV. We have completed the analysis of all DRB1, DRB3, DRB4 and DRB5 alleles for 70 patients with breast cancer (only some of whom overlap with our previous 72 patients). Of the 70 breast cancer samples included in our freshly initiated studies we consider data from 3 to be unreliable. These samples are currently being reanalysed along with the next batch of breast cancer DNAs. A complete listing of the individual genotypes of the breast cancer patients is presented in Table V.

CONCLUSIONS

Detailed molecular typing of DPB, DQB, and DRB1, 3, 4, and 5 alleles was performed on 144 controls. DNA was isolated from 70 freshly selected and cultured lymphoblastoid cell lines derived from patients with breast cancer. Molecular typing of DRB1, 3, 4, and 5 alleles was also been performed on these patients. While preliminary results support earlier studies indicating a high frequency of DRB1*0701 in patients with breast cancer, clearly a larger analysis must be completed before attempting to statistically evaluate this information.

APPENDICES (TABLES I-V)

TABLE I

DPB1 ALLELES IN CONTROLS (n=93)

| | |
|------------|------------|
| DPB1*0101 | 7.8% (7) |
| DPB1*0201 | 18.9% (17) |
| DPB1*0202 | 1.1% (1) |
| DPB1*0301 | 20.0% (18) |
| DPB1*0401 | 50% (45) |
| DPB1*0402 | 30.0% (27) |
| DPB1*0501 | 0.0% (0) |
| DPB1*0601 | 2.2% (2) |
| DPB1*0801 | 1.1% (1) |
| DPB1*0901 | 0.0% (0) |
| DPB1*1001 | 7.8% (7) |
| DPB1*1101 | 2.2% (2) |
| DPB1*1301 | 4.4% (4) |
| DPB1*1401 | 4.4% (4) |
| DPB1*1501 | 3.3% (3) |
| DPB1*1601 | 0.0% (0) |
| DPB1* 1701 | 2.2% (2) |
| DPB1*1801 | 1.1% (1) |
| DPB1*1901 | 1.1% (1) |

TABLE I (Continued)

| | |
|-----------|------------|
| DPB1*2001 | 7.8% (7) |
| DPB1*2101 | 0.0% (0) |
| DPB1*2201 | 0.0% (0) |
| DPB1*2301 | 20.0% (18) |
| DPB1*2401 | 0.0% (0) |
| DPB1*2501 | 1.1% (1) |
| DPB1*2601 | 0.0% (0) |
| DPB1*2701 | 3.3% (3) |
| DPB1*2801 | 0.0% (0) |
| DPB1*2901 | 1.1% (1) |
| DPB1*3001 | 0.0% (0) |
| DPB1*3101 | 0.0% (0) |
| DPB1*3201 | 0.0% (0) |
| DPB1*3301 | 0.0% (0) |
| DPB1*3401 | 0.0% (0) |
| DPB1*3501 | 2.2% (2) |
| DPB1*3601 | 1.1% (1) |

TABLE II**DQB1 ALLELES IN CONTROLS (n=86)**

| | |
|------------|------------|
| DQB1*0201 | 24.4% (21) |
| DQB1*0301 | 46.5% (40) |
| DQB1*0302 | 19.8% (17) |
| DQB1*03031 | 0.0% (0) |
| DQB1*03032 | 9.3% (8) |
| DQB1*0401 | 0.0% (0) |
| DQB1*0402 | 4.7% (4) |
| DQB1*0501 | 18.6% (16) |
| DQB1*0502 | 4.7% (4) |
| DQB1*05031 | 9.3% (8) |
| DQB1*05032 | 0.0% (0) |
| DQB1*0504 | 0.0% (0) |
| DQB1*0601 | 1.2% (1) |
| DQB1*0602 | 26.7% (23) |
| DQB1*0603 | 11.6% (10) |
| DQB1*0604 | 4.7% (4) |
| DQB1*0605 | 0.0% (0) |

TABLE III**DRB1 ALLELES IN CONTROLS (n=93)**

| | | |
|-----|-----------|------------|
| DR1 | *0101 | 10.8% (10) |
| | *0102 | 6.5% (6) |
| | *0103 | 4.3% (4) |
| DR2 | *1501 | 25.8% (24) |
| | *1502 | 1.1%(1) |
| | *1503 | 0.0% (0) |
| | *1601 | 4.3% (4) |
| | *1602 | 0.0% (0) |
| DR3 | * 0301-02 | 17.2% (16) |
| DR4 | *0401 | 12.9% (12) |
| | *0402 | 6.5% (6) |
| | *0403 | 2.2% (2) |
| | *0404 | 5.4% (5) |
| | *0405 | 0.0% (0) |
| | *0406 | 0.0% (0) |
| | *0407 | 5.4% (5) |
| | *0408 | 1.1% (1) |
| | *0409 | 0.0% (0) |
| | *0410 | 0.0% (0) |

| | | |
|------|----------|------------|
| | *0411 | 0.0% (0) |
| DR7 | *0701 | 16.1% (15) |
| DR8 | *0801-04 | 4.3% (4) |
| DR9 | *0901A/B | 1.1% (1) |
| DR10 | *1001 | 1.1% (1) |
| DR11 | *1101 | 15.0% (14) |
| | *1102 | 1.1% (1) |
| | *1103 | 2.2% (2) |
| | *1104 | 8.6% (8) |
| DR12 | *1201-02 | 5.4% (5) |
| DR13 | *1301 | 10.8% (10) |
| | *1302 | 5.4% (5) |
| | *1303 | 1.1% (1) |
| | *1304 | 0.0% (0) |
| | *1305 | 0.0% (0) |
| DR14 | *1401 | 9.7% (9) |
| | *1402 | 0.0% |

| | |
|-------|----------|
| *1403 | 1.1% (1) |
| *1404 | 2.2% (2) |
| *1405 | 0.0% (0) |
| *1406 | 0.0% (0) |
| *1407 | 0.0% (0) |
| *1408 | 0.0% (0) |

TABLE IV

DRB3, DRB4 and DRB5 ALLELES IN CONTROLS (n=93)

DRB3

| | |
|-------------|------------|
| *0101 | 23.7% (22) |
| *0201/*0202 | 46.2% (43) |
| *0301 | 5.4% (5) |

DRB4

| | |
|-------|------------|
| *0101 | 45.2% (42) |
|-------|------------|

DRB5

| | |
|-----------|------------|
| *0101 | 28.0% (26) |
| *0102/*02 | 3.2% (3) |

| TABLE V | I.D.# | MHC DRB1 | MHC DRB1 | MHC DRB3/4/5 | MHC DRB3/4/5 |
|--|--------|----------|----------|--------------|--------------|
| | | allele | allele | allele | allele |
| GENOTYPING OF BREAST CANCER SUBJECTS | Brl 04 | * 1601 | * 0102 | DRB4 * 0101 | DRB5 * 0101 |
| | Brl 10 | * 0402 | — | DRB4 * 0101 | DRB3 * 02 |
| | Brl 08 | * 14 | * 04 | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 11 | * 08 | — | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 12 | * 0302 | * 15 | DRB3 * 0101 | DRB5 * 0101 |
| | Brl 13 | * 1501 | — | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 15 | * 0103 | * 15 | DRB3 * 0202 | DRB5 * 0101 |
| | Brl 17 | * 0103 | * 0103 | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 18 | * 0302 | — | — | — |
| | Brl 30 | * 1403 | — | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 34 | * 07 | * 1403 | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 36 | * 1302 | * 1501 | DRB3 * 0101 | DRB5 |
| | Brl 37 | * 0302 | — | DRB4 * 0101 | |
| | Brl 39 | * 0402 | * 0302 | DRB3 * 0101 | DRB4 * 0101 |
| | Brl 42 | * 07 | * 1403 | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 47 | * 0101 | * 07 | DRB4 * 0101 | |
| | Brl 52 | * 0401 | * 1302 | DRB3 * 0301 | DRB4 * 0101 |
| | Brl 54 | * 1501 | * 0401 | DRB4 * 0101 | |
| | Brl 55 | * 1501 | * 0401 | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 56 | * 1303 | * 1303 | DRB3 * 0101 | DRB3 * 0101 |
| | Brl 57 | * 0102 | * 0302 | DRB3 * 0101 | DRB4 |
| | Brl 61 | * 04 | — | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 63 | * 1302 | * 0302 | DRB3 * 02 | |
| | Brl 65 | * 0401 | * 1302 | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 68 | * 0401 | * 0302 | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 70 | * 0401 | * 14 | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 71 | * 07 | * 1202 | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 72 | — | — | DRB4 * 0101 | |
| | Brl 74 | * 1501 | * 0407 | DRB3 * 0202 | DRB5 * 0101 |
| | Brl 75 | * 04 | * 1602 | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 77 | * 0302 | — | DRB3 * 0202 | DRB5 * 0101 |
| | Brl 78 | — | — | DRB3 * 0202 | DRB5 * 0101 |
| | Brl 81 | * 0101 | * 07 | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 83 | * 04 | * 0302 | DRB3 * 0101 | DRB4 * 0101 |
| | Brl 85 | * 0404 | * 1403 | DRB3 * 0202 | DRB4 * 0101 |
| | Brl 88 | * 07 | * 1503 | DRB3 * 0201 | DRB5 * 0101 |
| | Brl 89 | * 1502 | — | DRB3 * 0201 | DRB5 * 0101 |
| | Brl 90 | * 1403 | — | DRB3 * 0202 | DRB5 * 01 |
| | Brl 93 | * 07 | * 1403 | DRB3 * 0202 | — |
| | Brl 95 | * 0405 | * 1302 | DRB3 * 0101 | — |
| | Brl 97 | * 07 | — | DRB3 * 0201 | — |
| | Brl 98 | * 1303 | — | DRB3 * 0101 | — |
| | Brl 99 | * 1302 | — | DRB3 * 0301 | — |

| I.D.# | MHC DRB1 allele | MHC DRB1 allele | MHC DRB3/4/5 allele | MHC DRB3/4/5 allele |
|---------|--------------------|--------------------|------------------------|------------------------|
| Brl 101 | * 07 | *0407 | DRB3 * 0202 | — |
| Brl 102 | * 0302 | * 1601 | DRB3 * 0202 | — |
| Brl 103 | * 0408 | *1501 | DRB3 * 0202 | DRB5 |
| Brl 104 | * 07 | * 0101 | DRB3 * 0202 | — |
| Brl 106 | * 0407 | * 0302 | DRB3 * 0101 | — |
| Brl 108 | * 1303 | — | DRB3 * 0101 | — |
| Brl 109 | * 07 | * 1403 | DRB3 * 0202 | — |
| Brl 111 | * 1503 | — | DRB3 * 1010 | DRB5 |
| Brl 112 | * 07 | * 1501 | DRB3 * 0202 | DRB5 |
| Brl 118 | * 1501 | * 1302 | DRB3 * 0101 | — |
| Brl 119 | * 0404 | * 1403 | DRB3 * 0202 | — |
| Brl 121 | * 07 | — | DRB3 * 0202 | — |
| Brl 122 | * 0302 | — | DRB3 * 0101 | — |
| Brl 123 | * 0407 | * 1302 | DRB3 * 0301 | — |
| Brl 124 | * 0302 | — | DRB3 * 0101 | — |
| Brl 125 | * 0302 | *0408 | DRB3 * 0301 | — |
| Brl 126 | * 1501 | * 0101 | DRB3 * 0202 | — |
| Brl 128 | * 0101 | * 1501 | DRB3 * 0202 | — |
| Brl 129 | * 1501 | * 0408 | DRB3 * 0202 | — |
| Brl 132 | * 0302 | — | DRB3 * 0101 | — |
| Brl 133 | * 1501 | * 1202 | DRB3 * 0202 | — |
| Brl 137 | * 1401 | — | DRB3 * 0202 | — |
| Brl 139 | * 1501 | — | DRB3 * 0202 | DRB5 |
| Brl 140 | * 1501 | * 0402 | DRB3 * 0201 | — |